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Socially defeated male rats display a blunted adrenocortical response to a low dose of 8-OH-DPAT

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Abstract

The study examined in male Wistar rats the influence of social defeat on the neuroendocrine stress response system using injection of the 5-HT_{1A} receptor agonist, 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT), as the pharmacological challenge. Social defeat was defined by the submissive postures displayed by the Wistar rats which were threatened and attacked by Tryon Maze Dull S3 rats for 10 min. 18–20 h after social defeat, the defeated rats were injected intravenously (i.v.) with a low and high dose of 8-OH-DPAT in their home cages. Blood samples were withdrawn from the freely moving cannulated rats for determination of plasma corticosterone and catecholamines. The corticosterone response to the low dose of 8-OH-DPAT (0.05 mg/kg, i.v.) was significantly diminished in the defeated rats as compared to the controls, but this dose failed to affect catecholamine concentrations. The high dose of 8-OH-DPAT (0.15 mg/kg, i.v.) significantly elevated corticosterone and adrenaline levels in defeated and control rats to the same extent, whereas no effect on noradrenaline was found. The present data thus indicate that social defeat blunts 5-HT_{1A} receptor-mediated adrenocortical activation probably via a decrease in the sensitivity of a population of postsynaptic 5-HT receptors.

Keywords: Social defeat; Corticosterone; 5-HT_{1A} receptor; Subsensitivity

1. Introduction

The consequences of social defeat on the behavioural, neuroendocrine and physiological responses in experimental animals has long been a focus of interest. Recent attention has been directed to short- and long-term changes that develop following defeat. Social defeat in male rats potentiates the behavioural signs of anxiety as measured in the elevated plus-maze (Heinrichs et al., 1992) and results after several weeks in the development of behavioural depression (Koolhaas et al., 1990). Social defeat also increases circulating corticosterone levels via enhanced release of hypothalamic corticotropin-releasing hormone (CRH) (Merlo Pich et al., 1993). Consistent with these behavioural and endocrine changes is the enhanced activity of the brain serotonin system induced by social stress. In a colony situation, higher plasma corticosterone levels in subordinate rats are associated with increased 5-HIAA/5-HT (5-hydroxyindolacetic acid/serotonin) ratios in a number of brain areas including the hypothalamus, which is indicative of an increased 5-HT turnover rate (Blanchard et al., 1993).

The central nervous system not only organizes the stress response, but also serves as a major target for the adrenal steroids. Corticosteroids and stress enhance 5-HT turnover in the raphe-hippocampal system (Van Loon et al., 1981; De Kloet et al., 1982) and result in down-regulation of 5-HT_1 receptor binding (Biegon et al., 1985; De Kloet et al., 1986) of the 5-HT_{1A} type in the hippocampus (Mendelson and McEwen, 1992). The steroids also decrease the expression of 5-HT_{1A} receptor mRNA (Chalmers et al., 1993; Meijer and De Kloet, 1994). Based on these observations it is hypothesized that social defeat resulting in increased corticosterone levels decreases the responsiveness to 5-HT_{1A} receptor stimulation.

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The present study was designed to test this hypothesis by examining the effect of the systemically administered 5-HT_{1A} receptor agonist, 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT), on hypothalamic-pituitary-adrenocortical activation. 8-OH-DPAT induces CRH and adrenocorticotropin hormone (ACTH) release (Calogero et al., 1989, 1990, 1993), which subsequently results in elevated plasma corticosteroid levels in rat and man (Haleem et al., 1989; Korte et al., 1991; Welch et al., 1993; Lesch et al., 1990). Moreover, repeated glucocorticoid treatment attenuates the corticosterone response to 8-OH-DPAT (Bagdy et al., 1989b: Haleem, 1992). We report here that rats suffering from social defeat display a blunted hypothalamic-pituitary-adrenocortical response to a relatively low dose of systemic 8-OH-DPAT.

2. Materials and methods

2.1. Animals

Male Wistar rats ($n = 31$), weighing 290–340 g at the beginning of the experiments, were used. Immediately after surgery the rats were separated and housed individually in Plexiglas cages (25 × 25 × 30 cm; l × w × h) on a 12-h light-dark regimen (light on between 08:00–20:00 h). Trained dominant Tryon Maze Dull (TMD) S3 rats were housed in a different room with a reversed light-dark cycle (light on between 21:30–09:30 h). The TMD S3 animals (6–12 months of age) were permanently housed in wooden cages (85 × 60 × 50 cm) with a female rat, which was sterilized by ligation of the oviducts. Room temperature was controlled (21 ± 2°C). All animals had free access to standard rat chow and tap water. The experiments were carried out between 10:00–14:00 h.

2.2. Surgery

A silicon heart catheter (0.95 mm o.d., 0.5 mm i.d.) was inserted through the right jugular vein of the animal, under halothane anaesthesia. This catheter was used for frequent blood sampling in undisturbed, freely moving rats. The subjects were allowed 1 week for post-surgery recovery.

2.3. Drug treatment

The 5-HT_{1A} receptor agonist, 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT), was dissolved in saline. Injections were given intravenously (i.v.) in a constant volume of 1.0 ml/kg. Two doses of the drug (0.05 mg/kg and 0.15 mg/kg) were used. The choice of this dose range was based upon a study of Chaouloff et al. (1990a).

2.4. Procedure and blood sampling

To study the consequences of social defeat, male Tryon Maze Dull (TMD) S3 rats were used as dominant animals. The TMD S3 males are known as spontaneously territorially aggressive animals and thereby dominant against intruders. During the confrontation with the experimental rat the female was removed from the cage. The experimental male Wistar rats were threatened and attacked by TMD S3 rats for 10 min, during which the intruders displayed submissive postures as a behavioural sign of defeat. The control rats were handled but not exposed to the dominants' room, because it is known that even the smell of dominants produces a neuroendocrine stress response (unpublished observations). Defeated and control rats were treated with 8-OH-DPAT (0.05 mg/kg and 0.15 mg/kg, i.v.) in their home cages 18–20 h after social defeat. The challenge study was performed under resting conditions in the Wistar rats' home cages. 1 h before the start of the experiment the animals were connected to a polyethylene blood sampling tube (0.4 m length, 1.45 mm o.d. and 0.75 mm i.d.). Blood samples of 0.45 ml were withdrawn for determination of plasma catecholamines and corticosterone levels. After each sample was taken a similar quantity of heparinized donor blood was returned to avoid diminution of the blood volume with related changes in hemodynamics. Donor blood was obtained from unstressed rats with permanent heart catheters. Blood samples were taken twice before drug treatment (i.e. −10 and −1 min) and at $T = 0$ min the animals were injected with 8-OH-DPAT (i.v.). Further blood samples were taken at 5, 10, 15, 20, 25, 30 min. The rats were treated and tested only once.

2.5. Chemical determinations

Blood samples were immediately transferred to chilled (0°C) centrifuge tubes containing 0.01% EDTA as antioxidant and 10 μl heparin solution (500 IU/ml) as anticoagulant. Blood was centrifuged at 4°C for 10 min at 5000 rpm, and 100 μl of the supernatant was stored at −20°C for corticosterone and at −70°C for the catecholamine measurements. Plasma corticosterone was measured by means of reversed-phase high-performance liquid chromatography (HPLC). Determination of plasma catecholamine concentrations was performed by HPLC in combination with electrochemical detection. The HPLC-ECD system included a LKB 2150 pump (LKB instruments, Bromma, Sweden), a Rheodyne injection valve with a 100-μl loop, a 25-cm analytical column (nucleosil C18, Macherey-Nagel, Gimex Ned), held at 40°C by a column stove (LKB), a 5100-A electrochemical detector with a 5020 guard cell and a 5011 high sensitivity detector cell (ESA), and a

BD 41 two-channel flat bed recorder (Kipp). The guard cell potential in front of the injection valve was + 450 mV, the potentials of the working electrodes of the detector cell were −50 and + 350 mV, respectively. The mobile phase contained 0.034 M citric acid, 0.043 M Na_2HPO_4, 0.07% heptanesulfonic acid-sodium salt, 0.02% EDTA and 3% methanol 97% H_2O (pH 4.1). Absolute detection levels for plasma adrenaline and plasma noradrenaline were 0.010 and 0.005 ng/ml, respectively.

2.6. Statistics

Statistical analysis of neuroendocrine data was carried out with the aid of an analysis of variance (ANOVA) with between (defeat & control) and repeated (time point) subject factors. In case of significant effects, the ANOVAs were followed by post hoc *t*-tests. The Wilcoxon matched pairs test was used to compare hormone levels after 8-OH-DPAT treatment with baseline hormone concentrations. A probability level of $P < 0.05$ was considered as significant.

3. Results

3.1. The effects of 8-OH-DPAT on plasma corticosterone in defeated and control rats

Fig. 1 shows that in defeated rats treatment with the lower dose of 8-OH-DPAT (0.05 mg/kg) resulted in a mild increase in plasma corticosterone concentrations at $T = 10$ and $T = 15$ min ($P < 0.05$), and a higher increase in the control rats at $T = 10$, 15, 20 and 25

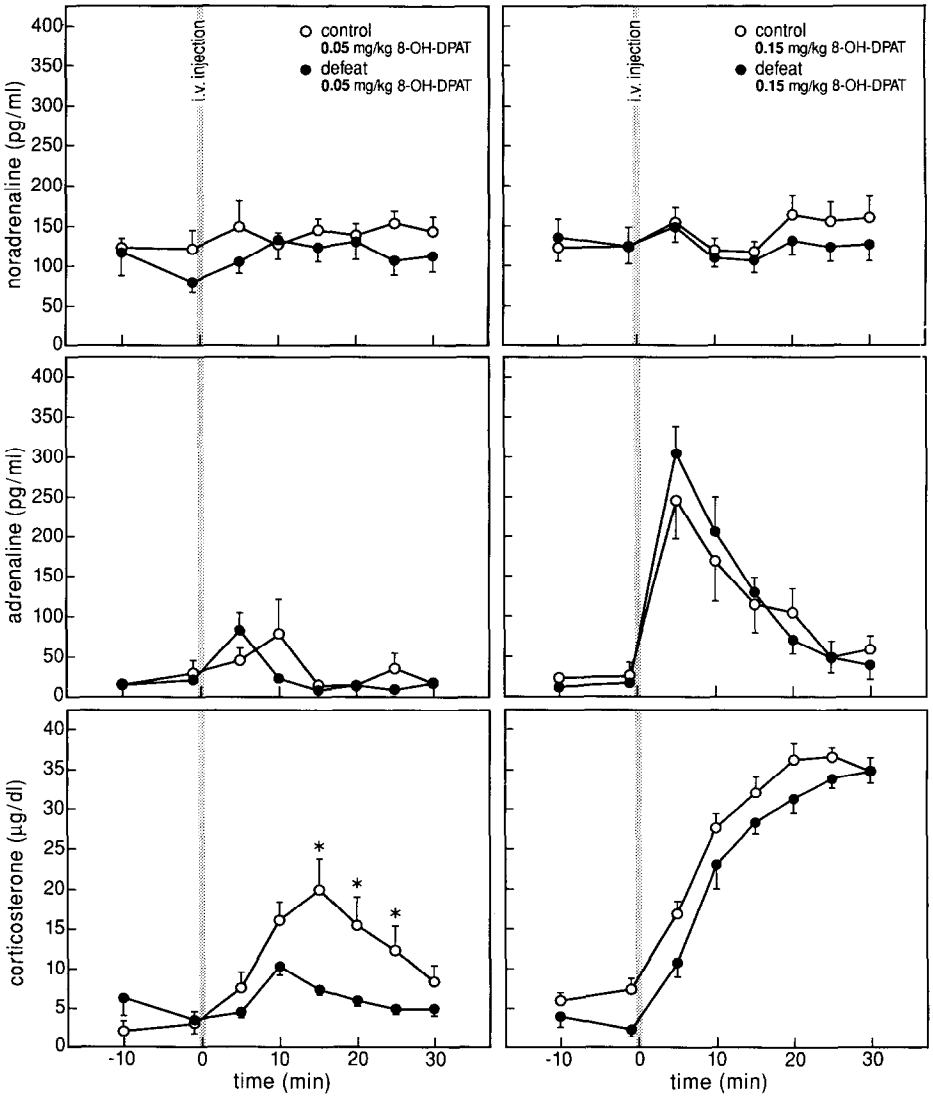

Fig. 1. Concentration of plasma corticosterone, adrenaline and noradrenaline after 5-HT_{1A} agonist 8-OH-DPAT treatment (0.05 mg/kg; and 0.15 mg/kg, intravenously (i.v.)) under resting conditions 18–20 h after social defeat (●) compared to controls (○).

min ($P < 0.01$), compared to baseline levels. A blunted plasma corticosterone response was seen in the defeated rats at 15, 20 and 25 min ($P < 0.05$) as compared to control rats. The ANOVA of plasma corticosterone data revealed a significant effect of social defeat, $F(1,12) = 4.82$; $P = 0.048$; a significant period effect, $F(7,84) = 13.22$; $P < 0.001$; and a significant period × prior defeat interaction $F(7,84) = 5.92$; $P < 0.001$. In both the defeated rats and the control rats, the higher dose of 8-OH-DPAT (0.15 mg/kg) led to an increase in plasma corticosterone concentrations at $T = 5$–30 min (at least $P < 0.05$), but both groups responded in a similar way. For the higher dose of 8-OH-DPAT the ANOVA of plasma corticosterone data revealed a significant period effect, $F(7,98) = 185.75$; $P < 0.001$, but no significant effect of prior defeat.

3.2. The effects of 8-OH-DPAT on plasma catecholamines in defeated and control rats

Fig. 1. also shows that treatment with 8-OH-DPAT had no effect on plasma noradrenaline concentrations either in the defeated or in the control rats. The plasma adrenaline levels also were not affected by the lower dose of 8-OH-DPAT (0.05 mg/kg). Treatment with the higher dose of 8-OH-DPAT (0.15 mg/kg), however, resulted in an increase in plasma adrenaline concentrations ($T = 5$, 10, and 15 min; at least $P < 0.05$) that was similar in both the defeated and the control rats. The ANOVA of plasma adrenaline data revealed no significant effect of prior defeat. A significant period effect was found, $F(7,105) = 38.81$; $P < 0.001$.

4. Discussion

The study demonstrated that social defeat leads to a condition of reduced adrenocortical activation after a 8-OH-DPAT challenge. The plasma corticosterone response to the low dose of the 5-HT_{1A} receptor agonist (0.05 mg/kg, i.v.) was significantly attenuated in the defeated rats compared to controls. The low dose of 8-OH-DPAT did not affect plasma catecholamine concentrations. The data were obtained in the home-cage environment of the rats indicating that the blunted response was the consequence of the earlier social stress for the serotonergic system.

A growing body of evidence indicates that postsynaptic 5-HT_{1A} receptors are involved in adrenocortical activation, because pretreatment with the serotonin synthesis inhibitor, *p*-chlorophenylalanine, in rats resulted in near total depletion of brain 5-HT content but had no effect on the ACTH rise induced by 8-OH-DPAT (Gilbert et al., 1988). Furthermore, 8-OH-DPAT increased CRH secretion from single explanted hypothalami (Calogero et al., 1989) and 8-OH-DPAT injected in the hypothalamic paraventricular nucleus increased plasma ACTH and corticosterone concentrations (Haleem et al., 1989; Korte et al., 1991; Welch et al., 1993). Prior administration of a 5-HT_{1A} receptor antagonist, (±)-pindolol, into the hypothalamic paraventricular nucleus completely blocked the ACTH release in response to systemically administered 8-OH-DPAT (Pan and Gilbert, 1992). Hypothalamic paraventricular nucleus lesions also completely block the 5-HT_{1A} induced corticosterone response (Bagdy et al., 1994). 8-OH-DPAT may cause ACTH release by stimulating both hypothalamic CRH (but not vasopressin) and pituitary ACTH secretion (Calogero et al., 1990, 1993). Therefore, it is suggested that postsynaptic 5-HT_{1A} receptors are involved in the present effects. It cannot be excluded, however, that subsensitivity of the presynaptic 5-HT_{1A} autoreceptors in the dorsal raphe nucleus also may have occurred.

It is assumed that the interactions between the glucocorticoids and the serotonergic system (De Kloet, 1991) altered the 5-HT_{1A} receptor-mediated response after social defeat. These interactions are complex, and stress, via corticosterone, may affect the serotonergic system through different mechanisms: (a) increase of the 5-HT synthesis and turnover in the dorsal raphe-hippocampal system (Van Loon, 1981; De Kloet et al., 1982); (b) down-regulation of 5-HT_{1A} receptor density in the dorsal raphe-hippocampus system (Biegon et al., 1985; De Kloet et al., 1986; Mendelson and McEwen, 1992; Tejani-Butt and Labow, 1994), which is exerted at the step of 5-HT_{1A} receptor transcription (Chalmers et al., 1993; Meijer and De Kloet, 1994); (c) direct effect on 5-HT signal transduction via: (i) glucocorticoid-dependent inhibition of G_i production (Harrington and Peroutka, 1990; Lesch and Lerer, 1991); (ii) suppression of serotonin-induced hyperpolarization of hippocampal CA1 neurons by low amounts of corticosterone, and subsequent reinstatement of this 5-HT response by high amounts of corticosterone (Joëls et al., 1991; Joëls and De Kloet, 1992). Collectively, these data suggest enhanced activity of the raphe-hippocampus system and down-regulated 5-HT_{1A} receptors. If down-regulated 5-HT_{1A} receptors also occur in the hypothalamic paraventricular nucleus, this may explain the reduced responsiveness to 8-OH-DPAT.

Indirect hypothalamic-pituitary-adrenocortical axis activation by stimulation of 5-HT_{1A} receptors, via a decrease in blood pressure, has been suggested (Saphier and Zhang, 1993). In our laboratory it has been shown that 1 day after social defeat, baseline blood pressure is lowered, whereas the blood pressure responses to psychosocial stimulation are increased (Fokkema et al., 1988). If changes in baseline blood pressure had been involved, further increases in plasma corticosterone would now have been expected in the defeated rats. In addition, the plasma corticosterone response to the low

dose of 8-OH-DPAT could not be explained by a secondary effect of adrenomedullary adrenaline release because no elevations in plasma catecholamine levels were seen.

At the high dose of 8-OH-DPAT (0.15 mg/kg, i.v.), higher but similar plasma corticosterone and adrenaline responses in control and defeated group were found, whereas no effects on plasma noradrenaline were seen. This is consistent with earlier findings (Bagdy et al., 1989a; Korte et al., 1991), that 8-OH-DPAT given in the hypothalamic paraventricular nucleus increased both plasma corticosterone and adrenaline but not noradrenaline concentrations. Prior administration of the 5-HT_{1A} receptor antagonist, (−)-pindolol, markedly diminished the rise in plasma adrenaline levels (Chaouloff et al., 1990a). Adrenaline release may participate in the elevation in plasma corticosterone levels that is elicited by 5-HT_{1A} receptor activation (Chaouloff et al., 1990b). Therefore, it cannot be excluded that, at high doses of 5-HT_{1A} receptor agonists, hypothalamic-pituitary-adrenocortical activity is masked by adrenergic mechanisms. These mechanisms may also be involved in the seemingly contradictory results we found with the systemically administered partial 5-HT_{1A} receptor agonist, ipsapirone, and/or its metabolite acting on α_2 receptors (Korte et al., 1990, 1992; Giral et al., 1987).

In summary, the day after defeat male Wistar rats displayed a blunted adrenocortical response after systemic administration of a low dose of 8-OH-DPAT in a stress-free home-cage, indicating a subsensitive 5-HT_{1A} receptor-effector system. Future studies should address the possible underlying mechanisms and the role of the interactions between the 5-HT and hypothalamic-pituitary-adrenocortical system. Also, changes in 5-HT_{1C} and 5-HT_2 receptor sensitivity are of interest, because these receptors are affected by stress and may activate the hypothalamic-pituitary-adrenocortical system (Van de Kar, 1989). The decrease found in pharmacological stimulation of the brain 5-HT_{1A} receptor after defeat may be of particular importance for the understanding of the pathophysiology of anxiety disorders and behavioral depression following a traumatic stress experience. Decreased hypothalamic-pituitary-adrenocortical axis activity after 5-HT_{1A} receptor challenge has been described in humans with unipolar depression and panic disorder (Lesch et al., 1990, Lesch, 1991), reflecting subsensitivity of the 5-HT_{1A} receptor-effector system.

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